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Primary care

Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study

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Abstract

Objective To determine which clinical variables provide diagnostic information in recognising heart failure in primary care patients with stable chronic obstructive pulmonary disease (COPD) and whether easily available tests provide added diagnostic information.

Design Cross sectional diagnostic study.

Setting 51 primary care practices.

Participants 1186 patients aged ≥65 years with COPD diagnosed by their general practitioner who did not have a diagnosis of heart failure confirmed by a cardiologist.

Main outcome measures Independent diagnostic variables for concomitant heart failure in primary care patients with stable COPD.

Results 405 patients (34% of eligible patients) underwent a systematic diagnostic investigation, which resulted in 83 (20.5%) receiving a new diagnosis of concomitant heart failure. Independent clinical variables for concomitant heart failure were a history of ischaemic heart disease, high body mass index, laterally displaced apex beat, and raised heart rate (area under the receiver operating characteristic curve (ROC area) 0.70, 95% confidence interval 0.64 to 0.76). Addition of measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) to the reduced "clinical model" had the largest added diagnostic value, with a significant increase of the ROC area to 0.77 (0.71 to 0.83), followed by electrocardiography (0.75, 0.69 to 0.81). C reactive protein and chest radiography had limited added value. A simplified diagnostic model consisting of the four independent clinical variables plus NT-proBNP and electrocardiography was developed.

Conclusions A limited number of items easily available from history and physical examination, with addition of NT-proBNP and electrocardiography, can help general practitioners to identify concomitant heart failure in individual patients with stable COPD.

Introduction

A diagnosis of heart failure in primary care is notoriously difficult, especially in the early phases and in the presence of chronic obstructive pulmonary disease (COPD).[1] Recognition of comorbid heart failure in patients with COPD is hampered by similarities in signs and symptoms and overlapping risk factors such as smoking. Echocardiography is essential to establish the diagnosis of heart failure. In many countries, however, accessibility to this diagnostic facility is limited in primary care.[2] In addition, high quality echocardiographic measurements are more difficult to obtain in patients with COPD.[3] Measurement of natriuretic peptides may be useful in the assessment of patients with suspected heart failure[4 5] and in those with acute dyspnoea.[6 7] However, diagnostic studies to determine the presence of heart failure in patients with stable COPD are lacking.

Most diagnostic studies, including those on the diagnosis of heart failure, are limited to evaluations of single tests.[8 9] In clinical practice, however, hardly any diagnosis is established by a single test. For example, history and physical examination are always considered before additional tests are ordered. Thus, studies are needed that use multivariable approaches to quantify which diagnostic tests truly contribute to the recognition of heart failure.[8 9]

We quantified which items from history and physical examination are potential diagnostic indicators of the presence or absence of heart failure in primary care patients with stable COPD. We also assessed whether easily available additional tests such as electrocardiography, chest radiography, and N-terminal pro-brain natriuretic peptide (NT-proBNP), provided added diagnostic value beyond history taking and physical examination.

Methods

Study population

Fifty one primary care practices in the Netherlands participated in this cross sectional study, which was carried out from April 2001 to June 2003. All practices routinely electronically registered their contacts with patients.[10] All patients aged ≥65 years with a registered International Classification of Primary Care (ICPC) code R91 (chronic bronchitis) or R95 (COPD or emphysema)[11] were eligible. These ICPC codes are based on symptoms (dyspnoea, cough, or sputum production) and, in case of R95, on pulmonary changes on chest radiography.[11] We excluded patients with a diagnosis of heart failure confirmed by a cardiologist and patients with severe psychiatric disorders, immobility, or terminal illness. In total 1186 eligible patients were invited by a letter signed by their own general practitioner, and 405 (34%) patients agreed to participate and signed informed consent. We extracted anonymised characteristics of all 1186 eligible patients from the computerised files.

Diagnostic investigation

The 405 participants underwent a three hour standardised diagnostic investigation at our outpatient clinic, including history, physical examination, electrocardiography (ECG), chest radiography, blood tests, pulmonary function tests, and echocardiography. We acquired data on comorbidities by scrutinising the general practices' computerised data files, including available letters from hospital specialists. One physician (FHR) took the patients' histories and carried out the physical examinations. Information on symptoms, smoking, and medication use was obtained by a questionnaire. Physical examination included measurement of jugular venous pressure and palpation of the apex beat in supine and lateral position. We classified unmeasurable jugular venous pressure (n = 13) as "non-elevated jugular venous pressure" and impalpable apex beat (n = 165) as "undisplaced apex beat." Blood samples were taken and analysed the same day. Eight patients had missing values for C reactive protein. After centrifugation, samples of serum and plasma were stored at −70°C. We measured serum concentrations of N-terminal pro B-type natriuretic peptide (NT-proBNP) with a non-competitive immunoradiometric assay (Roche, Mannheim, Germany) for all participants in a single batch. Two patients had missing values for NT-proBNP.

One cardiologist (M-JMC) recorded a standard 12 lead electrocardiogram and classified the result according to the Minnesota coding criteria.[12] One of three radiologists subsequently took and classified chest radiographs with standard procedures. Cardiothoracic ratio could not be measured in four patients because of lobectomy. Lung volumes, bronchodilator responses, airway resistance, alveolar volume, and diffusion capacity of the lung for carbon monoxide were measured with a fixed volume body plethysmograph and Masterscreen (Masterlab Jaeger, Würzburg, Germany). One pulmonologist (J-WJL) classified the results.

Finally, two cardiac sonographers performed echocardiographic studies using a Philips Sonos 5500 imaging system (Andover, MA). One cardiologist (M-JMC) interpreted the results. Parameters from Doppler analysis, M-mode echocardiography, and two dimensional transthoracic echocardiography were used. The left ventricular ejection fraction was calculated with Simpson's rule (disc summation method),[13] the single plane area-length method,[14] or semiquantitatively by two dimensional visual estimate ("eyeballing").[15] In 42 patients (10.4%) the image was of poor quality, and in one image we could not estimate left ventricular ejection fraction. Left atrial volume was assessed by the volume prolated ellipsoid method.[16] We used pulsed wave Doppler to measure the E and A wave velocity and E deceleration time and calculated the E/A velocity ratio. We recorded the flow velocities of the left or right upper pulmonary vein and calculated the ratio of systolic to diastolic forward flow. Diastolic function was categorised as normal, impaired relaxation, pseudonormal filling, or restrictive filling by a combination of transmitral and pulmonary flow patterns and left atrial volumes.[17–19] After all tests had been completed, the same cardiologist (M-JMC) re-assessed a random sample of 41 (10%) digitally stored echocardiograms, blinded to the original results. Only in two cases did he disagree with his original assessment (Cohen's $\kappa = 0.90$) when he changed his assessment of presence or absence of systolic or "isolated" diastolic dysfunction. In both cases the disagreement was between "normal" and impaired relaxation (grade I diastolic dysfunction).

Chest radiographs, pulmonary function tests, electrocardiograms, and echocardiograms were interpreted without knowledge of other data.

Presence or absence of heart failure

Ideally, in studies of diagnostic accuracy the final diagnosis is made by a (single) reference test, without knowledge of the results of the test(s) under study.[8 9 20–22] Although echocardiography is a cornerstone in the diagnosis of heart failure, it is still considered imperfect as a reference test (that is, the "gold standard").[2] The best alternative for diagnostic accuracy studies of diseases that lack an established reference is the use of consensus diagnosis as reference.[9 21 22] In our study, an expert panel determined the presence or absence of heart failure as in previous studies.[4 6 23] Our panel comprised two cardiologists, a pulmonologist, and a general practitioner. In case of no consensus the majority decided whether the case definition was met. In case of evenly split votes (which occurred in five patients) we used the majority decision of the two cardiologists and the general practitioner. The panel used all available information from the diagnostic investigation, including echocardiography, except NT-proBNP results.

Patients with heart failure were further classified as having systolic, "isolated" diastolic, or "isolated" right sided heart failure. For systolic heart failure, patients had to have an echocardiographic left ventricular ejection fraction $\leq 45\%$ in combination with presence of symptoms indicative of heart failure (such as orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, peripheral oedema, nocturia more than twice a night, or any combination of these symptoms). For isolated diastolic ventricular dysfunction, patients had to have echocardiographic diastolic dysfunction and a left ventricular ejection fraction $>45\%$. For isolated diastolic heart failure patients had to have echocardiographic diastolic abnormalities in combination with indicative symptoms and signs (such as peripheral or pulmonary fluid retention or raised jugular venous pressure) of heart failure[24] or indicative symptoms and echocardiographic left ventricular hypertrophy, atrial fibrillation, or anginal complaints.[25]

We defined isolated right sided heart failure as increased right atrial pressure, estimated from the respiratory variation in diameter of the caval vein or right ventricular dysfunction assessed semiquantitatively by the two dimensional visual estimate method, or both, and a left ventricular ejection fraction $>45\%$.

Data analysis

We quantified the relation of each diagnostic variable or test with the presence or absence of heart failure using univariable logistic regression analysis. Variables with a P value <0.15 were included in multivariable logistic regression analyses to determine their independent contribution to the diagnosis of heart failure. In this multivariable analyses we followed the chronology in which investigations are performed in practice.[8 9 26] Firstly, we included all findings from the history and physical examination. This "clinical model" was then reduced by excluding variables (one by one) from the model with P values >0.10 based on the likelihood ratio test, yielding a reduced clinical model. We then added results of laboratory tests (such as NT-proBNP and C reactive protein), electrocardiography, and chest radiography (first separately and then in different combinations) to quantify their added diagnostic value, again with the likelihood ratio test at a $P>0.10$, and so constructed a final model. We calculated sensitivity, specificity, and the predictive values with 95% confidence intervals for the variables included in the final model, applying clinically relevant and previously published cut off values for the continuous variables.[27 28] We did not evaluate echocardiographic variables on their independent diagnostic value because we conducted the study

Table 1 Characteristics of eligible patients with general practitioner's diagnosis of COPD, according to participation in study. Values are numbers (percentages) of patients unless stated otherwise

Characteristics	Participants (n=405)	Non-participants (n=781)	P value
Mean (SD) age (years)	73.0 (5.3)	74.9 (7.8)	<0.001
Male	223 (55.1)	420 (53.8)	0.67
Ischaemic heart disease*	82 (20.2)	190 (24.3)	0.11
Hypertension	145 (35.8)	291 (37.3)	0.62
Diabetes mellitus	42 (10.4)	100 (12.8)	0.22
Stroke/TIA	21 (5.2)	61 (7.8)	0.09
Atrial fibrillation	34 (8.4)	71 (9.1)	0.69
Valvular disease	14 (3.5)	37 (4.7)	0.30
Other chronic pulmonary diseases†	94 (23.2)	190 (24.3)	0.67
Also treated by cardiologist	63 (15.6)	158 (20.2)	0.05
Also treated by pulmonologist	135 (33.3)	241 (30.9)	0.39

TIA=transient ischaemic attack.
*Presence of ischaemic heart disease including myocardial infarction, angina pectoris, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI).
†Including (persistent) asthma, pulmonary cancer, bronchiectasis, tuberculosis, alveolitis, sarcoidosis, idiopathic pulmonary fibrosis, pulmonary hypertension, and pneumothorax. No eligible patient had α_1 antitrypsin deficiency.

with a view to primary and pulmonary care, where echocardiography is not routinely available. Moreover, echocardiography would probably have had over-riding weight in the assessment and thus would over-rule the contribution of all other tests in the multivariable analysis.[22]

We used the area under the receiver operating characteristic curve (ROC area) to estimate the ability of models to discriminate between patients with and without heart failure.[26]

Results of any model will be too optimistic when the model is used on the dataset from which it was developed, so called over-fitting.[9 26 29] We therefore used bootstrapping techniques, repeating the entire modelling process (including the variable selection), to validate the final model and to adjust (shrink) the estimated performance (ROC area) and regression coefficients (log odds ratios) for over-fitting.[26] The performance of a model after bootstrapping is more in concordance with the performance that can be expected in future patients.

To construct an easy applicable diagnostic rule or points score, we transformed the original regression coefficients (after adjustment for over-fitting) of the variables in the final model to integers according to their relative contributions to the risk estimation. Finally, after estimating the score for each patient, we estimated the absolute percentages of correctly diagnosed patients across score categories. All calculations were performed using S-PLUS version 6.1 (Insightful Corp, Seattle, WA).

Nine participants had 14 missing values (two NT-proBNP, eight C reactive protein, four cardiothoracic ratio). Missing data usually do not occur at random. As deletion of subjects with a missing value (so called "complete case analysis") may lead to biased results and loss of power,[26 30 31] we imputed any missing values by using a regression method with the addition of a random error term (SPSS software, version 12.0 for Windows, SPSS, Chicago, IL).[26 30 31] The imputation was based on the correlations between each variable with missing values and all other variables as estimated from the 391 (97%) complete datasets.

Results

Eligible patients participating in the study (n=405, 34%) were 1.9 years younger than non-responders (n=781, 66%) and healthier overall (table 1). The median age of the study population was 73 (SD 5.3) years, and 55% were male.

In 83 patients (20.5%) the consensus panel set a new diagnosis of heart failure. Of these, 42 patients had systolic and 41 had isolated diastolic heart failure. There were no cases of isolated right sided heart failure. All 41 patients with isolated diastolic heart failure had symptoms indicative of heart failure. In addition to these symptoms, 22 patients had also indicative signs of heart failure, four patients had atrial fibrillation, eight patients had echocardiographic left ventricular hypertrophy, two patients had angina and five patients had a combination of atrial fibrillation, left ventricular hypertrophy, or angina.

Re-presenting (blinded to the original decision) a random sample of 41 (10%) patients to the panel showed disagreement in one case only (Cohen's $\kappa=0.92$). This patient had moderate-severe dyspnoea, indicative symptoms and signs of heart failure, atrial fibrillation, a slightly impaired echocardiographic left ventricular ejection fraction of 45-50%, and a normal diastolic function. This patient was originally classified as not having heart failure and subsequently reclassified as having heart failure.

Of all participants, only three had an S3-gallop, and 11 patients had signs of pulmonary fluid on chest radiography. One participant had a serum creatinine concentration >200 μmol/l (243 μmol/l), and no participant had a blood urea >20 mmol/l.

Table 2 shows the univariable associations. Electrocardiographic abnormalities were more common in those with heart failure, mostly ST or T wave abnormalities, or both (22.7%), left bundle branch block (complete or incomplete) (16.1%), and Q waves suggesting a previous myocardial infarction (7.7%). Results from pulmonary function tests were similar in patients with and without heart failure.

Of the variables from history and physical examination with a univariable $P<0.15$, only history of ischaemic heart disease (odds ratio 2.16), a laterally displaced apex beat (2.34), body mass index (BMI) (1.11 per kg/m^2), and heart rate (1.26 per 10 beats/minute) were independent clinical predictors of presence of heart failure in multivariable analysis and included in the "clinical" model (table 3). Cardiovascular medication (such as diuretics or angiotensin converting enzyme inhibitors) was not an independent predictor.

NT-proBNP (odds ratio 1.06 per 5 pmol/l) was the best single diagnostic test when applied without information from the clinical assessment with an ROC area of 0.72 (0.66 to 0.79, $P<0.001$). Addition of NT-proBNP to the four clinical items significantly increased the ROC area from 0.70 to 0.77 (table 3). Addition of electrocardiography to the clinical model increased the ROC area significantly from 0.70 to 0.75, and addition of C reactive protein or cardiothoracic ratio increased it to 0.73 (table 3). Addition of an abnormal electrocardiogram to the clinical+NT-proBNP model was also significantly associated with presence of heart failure (odds ratio 2.75) (table 4). When added to the clinical plus NT-proBNP model, C reactive protein (1.03 per mg/l, 1.00 to 1.07, $P=0.09$) and cardiothoracic ratio (1.05 per unit, 1.00 to 1.07, $P=0.11$) were borderline associated with presence of heart failure and did not change the ROC area. Hence, our final model included a history of ischaemic heart disease, a laterally displaced apex beat, high body mass index, raised heart rate, NT-proBNP, and abnormal electrocardiogram (table 3). Table 4 shows the diagnostic accuracy of the independent predictors in the final model.

Using the formula of the final model in table 3, we can estimate a patient's probability of heart failure based on his or her clinical profile and the NT-proBNP and result of electrocardiography. The ROC area was 0.76 (table 3). To facilitate use in daily care, we simplified the final model to an easy applicable scoring rule. Regression coefficients of the variables of the final model

Table 2 Characteristics of participants according to presence or absence of heart failure and results of univariable analysis. Values are numbers (percentages) unless stated otherwise

Characteristics	Heart failure (n=83)	No heart failure (n=322)	Odds ratio (95% CI)	P value
History				
Median (IQR) age (years)	74 (69-78)	72 (69-76)	1.04 (1.00 to 1.09)*	0.07
Median (IQR) pack years of smoking†	25.0 (1.1-41.7)	15.0 (0.0-38.1)	1.01 (1.00 to 1.02)*	0.04
Ischaemic heart disease‡	28 (33.7)	55 (17.1)	2.47 (1.44 to 4.24)	0.001
Cardiovascular comorbidity§	51 (61.4)	144 (44.7)	1.97 (1.20 to 3.23)	0.007
Orthopnoea or paroxysmal nocturnal dyspnoea	25 (30.1)	83 (25.8)	1.24 (0.73 to 2.11)	0.43
Nocturia (≥ twice/ night)	45 (54.2)	130 (40.4)	1.75 (1.08 to 2.84)	0.02
Medication				
Diuretics	29 (34.9)	71 (22.0)	1.90 (1.13 to 3.20)	0.02
ACE inhibitors	22 (26.5)	50 (15.5)	1.96 (1.11 to 3.48)	0.02
Physical examination				
Mean (SD) BMI (kg/m^2)	28.1 (3.9)	26.3 (4.2)	1.10 (1.04 to 1.17)*	0.001
Mean (SD) heart rate (beat/minute)	80.0 (15.9)	75.6 (13.5)	1.02 (1.01 to 1.04)*	0.01
Pulmonary sounds¶	31 (37.3)	97 (30.1)	1.38 (0.84 to 2.29)	0.21
Raised jugular venous pressure	26 (31.3)	75 (23.3)	1.56 (0.91 to 2.66)	0.10
Laterally displaced apex beat	22 (26.5)	48 (14.9)	2.06 (1.16 to 3.66)	0.01
Peripheral oedema	22 (26.5)	54 (16.8)	1.79 (1.01 to 3.16)	0.04
Additional tests				
Median (IQR) NT-proBNP (pmol/l)	28.9 (15.1-95)	13.2 (8.3-23.3)	1.01 (1.01 to 1.02)*	<0.001
Median (IQR) C reactive protein (mg/ml)	5.0 (3.0-10.0)	3.0 (3.0-6.0)	1.05 (1.02 to 1.09)*	0.001
Mean (SD) cardiothoracic ratio	0.50 (0.05)	0.47 (0.05)	1.10 (1.05 to 1.15)*	<0.001
Abnormal ECG**	52 (62.7)	91 (28.3)	4.26 (2.57 to 7.07)	<0.001
Mean (SD) FEV_1 as % of expected††	81.7 (24.2)	83.7 (25.9)	0.74 (0.28 to 1.91)	0.53
Mean (SD) FEV_1/FVC††	65.3 (13.1)	64.1 (14.4)	1.01 (0.99 to 1.02)	0.50
FEV_1/FVC <70%††	50 (60.2)	194 (60.2)	1.00 (0.61 to 1.64)	1.00

IQR=interquartile range; BMI=body mass index.
*Odds ratio per unit change.
†In current and former smokers.
‡Including myocardial infarction, angina pectoris, percutaneous coronary intervention, or coronary artery bypass grafting.
§Diabetes mellitus, hypertension, stroke, or peripheral arterial disease.
¶Crackles, including crepitations, and wheezing.
**Suggesting diagnosis of (previous) myocardial infarction (abnormal Q waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T wave abnormalities, and sinus tachycardia.
††Post-dilatory spirometric measurements were used. In five cases with missing values due to interruption of pulmonary measurements, pre-dilatory values were used. For expected values (reference values) of forced expiratory volume in 1 second (FEV_1), we used recommendations of European Respiratory Society.[51]

Table 3 Independent contribution according to multivariable analysis of tests from history, physical examination, and additional tests to diagnosis of heart failure in patients with general practitioner's diagnosis of COPD

Variables	Odds ratio (95% CI)	P value	ROC area of model (95% CI)	Points for rule*
Clinical model				
History of ischaemic heart disease	2.16 (1.28 to 3.64)	0.004	0.70 (0.64 to 0.76)	
Body mass index (per kg/m^2)	1.11 (1.04 to 1.18)	0.001		
Laterally displaced apex beat	2.34 (1.28 to 4.29)	0.006		
Heart rate (per 10 beats/minute)	1.26 (1.06 to 1.49)	0.009		
Clinical model plus additional tests				
Clinical model+NT-proBNP (per 5 pmol/l)	1.05 (1.03 to 1.07)†	<0.001	0.77 (0.71 to 0.83)	
Clinical model+ ECG‡	3.69 (2.17 to 6.29)†	<0.001	0.75 (0.69 to 0.81)	
Clinical model+ C reactive protein (per mg/ml)	1.05 (1.02 to 1.08)†	0.003	0.73 (0.67 to 0.79)	
Clinical model+ cardiothoracic ratio (per unit)	1.08 (1.02 to 1.13)†	0.005	0.73 (0.67 to 0.79)	
Clinical model+ NT-proBNP + ECG‡	2.75 (1.54 to 4.92)†	0.001	0.78 (0.72 to 0.84)	
Final model§¶				
History of ischaemic heart disease	1.57 (0.90 to 2.74)	0.06	0.76 (0.70 to 0.81)	2
Body mass index >30 kg/m^2	2.14 (1.15 to 3.99)	0.004		3
Laterally displaced apex beat	2.05 (1.08 to 3.91)	0.008		3
Heart rate >90 beats/minute	1.59 (0.81 to 3.11)	0.10		2
NT-proBNP >14.75 pmol/l**	2.68 (1.45 to 4.97)	0.001		4
Abnormal ECG‡	2.07 (1.17 to 3.65)	0.003		3

ROC area=area under receiver operating characteristic curve; ECG=electrocardiogram.
*Regression coefficients of variables of final model rounded to integers according to their relative contribution to risk estimation. Subsequently, for each patient total points were estimated by this scoring rule.
†Odds ratios (95% CI) and P values given for additional test only when added to clinical model.
‡Suggesting diagnosis of (previous) myocardial infarction (abnormal Q waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T wave abnormalities, and sinus tachycardia.
§After dichotomising continuous variables at clinically relevant and previously published thresholds,[27 28] and after adjustment of regression coefficients (odds ratios) and ROC area for over-fitting based on bootstrapping techniques.
¶Probability of heart failure as estimated by final model=1/(1+exp–(–2.83+0.45*history of IHD+0.76*BMI>30 kg/m^2+0.72*displaced apex beat+0.46*heart rate >90 beats/min+0.99*NTproBNP >14.75 pmol/l (>125 pg/ml)+0.73*abnormal ECG)), in which –2.83 is intercept and other numbers are regression coefficients (log (OR)) adjusted for over-fitting based on bootstrapping techniques.
**Equivalent to >125 pg/ml.

were rounded to integers according to their relative contribution to the risk estimation (see table 3, last column). Subsequently, for each patient the total points were estimated by this scoring rule. The total score of the patients ranged from 0-14 points. The observed prevalence of heart failure among very low risk patients (0 points) was 4.9% (4 out of 81 patients), 10.6% (15 out of 142 patients) among low risk (2-5 points), 25.4% (32 out of 126 patients) among medium risk (6-9 points), and 57.1% (32 out of 56 patients) among high risk patients (10-14 points) (table 5). Dichotomising the scale at, for example, 9 points (at ≤ 9 points the diagnosis is negative and >9 it is positive) yielded a positive predictive value of 57.1% and a negative predictive value of 85.4% (table 5).

Discussion

A history of ischaemic heart disease, a laterally displaced apex beat, a high body mass index, and a raised heart rate are independent clinical indicators of the presence of concomitant heart failure in elderly patients with stable COPD. Raised NT-proBNP and abnormalities on electrocardiography may further improve the diagnostic accuracy. The added value of C reactive protein or cardiothoracic ratio on chest radiograph is limited. To our knowledge, this is the first study to determine the

Table 4 Unadjusted sensitivity, specificity, and predictive values of variables in final model

Variables*	Heart failure (n=83)	No heart failure (n=322)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
IHD present†	28	55	0.34 (0.24 to 0.45)	0.83 (0.78 to 0.87)	0.38 (0.27 to 0.50)	0.81 (0.76 to 0.85)
BMI >30 kg/m^2	27	51	0.33 (0.23 to 0.44)	0.84 (0.80 to 0.88)	0.35 (0.24 to 0.46)	0.83 (0.76 to 0.85)
Heart rate >90 beats/min	20	44	0.24 (0.15 to 0.35)	0.86 (0.82 to 0.90)	0.31 (0.20 to 0.44)	0.82 (0.77 to 0.86)
Displaced apex beat	22	48	0.27 (0.17 to 0.37)	0.85 (0.81 to 0.89)	0.31 (0.21 to 0.44)	0.82 (0.77 to 0.86)
NT-proBNP >14.75 pmol/l‡	65	140	0.78 (0.68 to 0.87)	0.56 (0.51 to 0.62)	0.32 (0.25 to 0.39)	0.91 (0.86 to 0.95)
Abnormal ECG	52	91	0.63 (0.51 to 0.73)	0.72 (0.66 to 0.77)	0.36 (0.28 to 0.45)	0.88 (0.84 to 0.92)

IHD=ischaemic heart disease; BMI=body mass index; ECG=electrocardiogram.
*For BMI, heart rate, and NT-proBNP we used clinically relevant and previously published cut off values.[27 28]
†Myocardial infarction, angina pectoris, percutaneous coronary intervention, or coronary artery bypass grafting.
‡Two missing values for NT-proBNP. 14.75 pmol/l NT-proBNP is equivalent to 125 pg/ml.

collective value of symptoms, signs, and additional testing to establish a diagnosis of heart failure in patients with COPD in primary care. Using six simple diagnostic indicators, the diagnosis of heart failure in these elderly patients can be improved.

Methodological aspects

In the diagnosis of heart failure there is no ideal standard. We used consensus diagnosis to assess the final diagnosis of heart failure, as in several previous studies.[4 6 9 22] A potential disadvantage of this reference method is the possibility of incorporation bias[22 32–34] because the reference standard (panel diagnosis) is not independent from all the tests studied. The effect of the incorporation bias can, however, be judged afterwards as it commonly leads to overestimation of the diagnostic value of the tests under study. Withholding results of crucial tests from the panel, however, leads to prevalent misclassification in the outcome (final diagnosis) with invalid estimates of the diagnostic value of the tests under study. We specifically chose to include most tests under study in the consensus judgment. Though echocardiography is the cornerstone of the diagnostic assessment of heart failure, we used this test only for assessing the outcome and not as a diagnostic test to prevent overestimation of its diagnostic value. In fact, any incorporation bias is likely to be small as most diagnostic determinants we studied were not crucial in the panel decision process. Furthermore, incorporation bias does not apply to NT-proBNP as this test was not included in the consensus diagnosis. Finally, in earlier studies, as in our study, panel diagnosis for establishing heart failure is highly reproducible[35 36] and it is, as stated by the Standards for Reporting of Diagnostic Accuracy (STARD) initiative, the best proxy reference in the absence of an ideal standard.[20]

Another issue regards the definition of diastolic heart failure. The echocardiographic variables needed to establish the diagnosis of diastolic heart failure are subject to debate. Therefore, we added clinical variables to increase the diagnostic accuracy of echocardiographic criteria, as suggested by others.[25 37]

We chose the definitions of test results to minimise indeterminate results of tests under study.[32] Only presence of increased jugular venous pressure or a laterally displaced apex beat could not be assessed in a relevant number of patients. By counting indeterminate as not present rather than present, however, we avoided overestimation of the diagnostic value.

We estimated the potential added diagnostic contribution of tests by the likelihood ratio test rather than the increase in ROC area, which is a rank order statistic and less sensitive for detecting small changes in diagnostic value between (reduced and extended) models.[26 38] Accordingly, electrocardiographic results (and to a lesser extent chest radiography and C reactive protein) were considered to have added value beyond history, physical examination, and NT-proBNP, even though the ROC area increased only marginally.

Validation of model

Although we adjusted the final model for over-fitting by applying bootstrapping techniques and shrinkage, this final model and the corresponding risk score needs to be validated externally in a new sample of primary care patients with COPD.[8 9 26]

Relation to other studies

Most independent tests for the presence or absence of concomitant heart failure in patients with COPD in our study have also been reported in studies among patients primarily suspected of heart failure.[4 5 39–41] Particularly, a history of ischaemic heart disease, or rather previous myocardial infarction, is an established diagnostic indicator for the presence of heart failure. Similarly, this applies to a laterally displaced apex beat, although the apex beat is impalpable in a substantial number of patients.[42] The diagnostic value of heart rate is controversial.[39] Perhaps the use of medication such as β sympathicometic inhaler drugs, often used by patients with COPD, may partly explain this finding. Our study is the first study to show that a high body mass index is independently related to the presence of heart failure in patients with COPD. Being overweight—that is, BMI ≥30—was already known to be a risk factor for the development of heart failure.[28] C reactive protein has not been examined for its diagnostic value before, although it is known to be related to atherosclerosis and an adverse prognosis in ischaemic heart disease.[43]

Natriuretic peptides

Importantly, the natriuretic peptide NT-proBNP was a powerful diagnostic test. As in other studies, we showed that NT-proBNP is

Table 5 Distribution of presence and absence of heart failure per score category of final model and corresponding sensitivity, specificity, and predictive values when dichotomised at different score thresholds*

Risk category of simplified model (points)	Heart failure (n=83)	No heart failure (n=322)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Very low (0), n=81	4	77				
Low (2-5), n=142	15	127	0.95 (0.88 to 0.99)	0.24 (0.19 to 0.29)	0.24 (0.20 to 0.29)	0.95 (0.88 to 0.99)
Medium (6-9), n=126	32	94	0.77 (0.67 to 0.86)	0.63 (0.58 to 0.69)	0.35 (0.28 to 0.43)	0.91 (0.87 to 0.99)
High (10-14), n=56	32	24	0.39 (0.28 to 0.50)	0.93 (0.89 to 0.95)	0.57 (0.43 to 0.70)	0.85 (0.81 to 0.89)

*As an example (see also table 3), patient with COPD with heart rate of 96 beats/minute (2 points), body mass index of 31 kg/m^2 (3 points), laterally displaced apex beat (3 points), and atrial fibrillation on the electrocardiogram (3 points) receives score of 11, corresponding to 57% risk (positive predictive value) of having heart failure.

most useful as a "rule out" test (high negative predictive value).[4–6] Overall diagnostic accuracy of the natriuretic peptide measurements in detecting heart failure, however, was lower than in previous studies of patients with suspected heart failure[4] and patients with acute dyspnoea visiting an emergency department,[6 44] but higher than levels reported in community screening studies with systolic or diastolic dysfunction, or both, as the outcome.[45 46] The most obvious reason for these differences in diagnostic accuracy are the difference in the populations studied.[45] We studied patients with a GP diagnosis of COPD, without a diagnosis of heart failure confirmed by a cardiologist. Patients with newly detected heart failure were therefore seen in an early stage of their disease. Moreover, our participants were in a stable phase. These aspects make it plausible that the concentrations of NT-proBNP are lower than, for instance, in patients with acute dyspnoea (acute increase in intracardiac pressure) or in whom the GP suspects heart failure,[46 47] because NT-proBNP production in the ventricles of the heart increases in response to increased intracardiac volume or pressure. Moreover, our patients with COPD without heart failure had a median NT-proBNP concentration of 13.2 pmol/l (interquartile range 8.3-23.3), which is at the upper level of the suggested normal range of 8.2-13.3 pmol/l.[27] Also other studies suggest that patients with COPD without heart failure can have increased concentrations of natriuretic peptide, possibly because of some degree of stress on the right ventricular wall.[48 49]

Applicability of results

The response rate in our study (34%) may seem modest but was only slightly lower than in population based studies assessing heart failure in elderly people.[23 50] Because we recruited elderly patients with stable COPD we would expect lower response rates as we invited many patients with rather high levels of disability. Although, inevitably, we studied only a selection of the available patients, selection bias seems unlikely because relevant and known cardiovascular risk factors for heart failure and comorbidities were only slightly lower in participants than in non-responders. Importantly, the clinical applicability of our results is high because we included those patients who were able to undergo the relevant diagnostic investigations—that is, patients in whom treatment is likely to be initiated in everyday practice.

In conclusion, several easily obtained clinical parameters and a few additional diagnostic investigations—notably, natriuretic peptide and electrocardiography—may improve the detection of concomitant heart failure in primary care patients with COPD. The use of these parameters should increase confidence about the diagnosis of heart failure and will help GPs to decide about the need for additional echocardiography or treatment in patients with COPD.

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Contributors: FHR led the design of the study, collected the data, performed the statistical analysis, participated in the panel, and wrote the first draft of the paper. KGMM participated in the design of the study, the statistical analyses, and the writing of the paper. M-JMC supervised the echocardiography, participated in the reproducibility study and in the panel, and edited the paper. DEG helped to obtain funding, participated in the design of the study, and edited the paper. NPAZ participated in the statistical analyses and edited the paper. J-WJL supervised the pulmonary function tests, participated in obtaining funding and in the panel, and edited the paper. AWH initiated the research, secured funding, and participated in the study design, the statistical analyses, and the writing of the paper. AWH and FHR are guarantors.

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What is already known on this topic

Several studies have assessed the value of signs and symptoms and additional tests such as natriuretic peptides and electrocardiography in recognising heart failure in patients in primary care or in patients with acute dyspnoea in hospital

Information on the diagnostic value of these items in a large group of patients with stable chronic obstructive pulmonary disease (COPD) is lacking

What this study adds

Four easily assessable clinical items (history of ischaemic disease, laterally displaced apex beat, high body mass index, and raised heart rate) provide independent diagnostic information about the presence or absence of concomitant heart failure in the individual primary care patient with COPD

The addition of natriuretic peptide measurements and electrocardiography further increases the accuracy of the diagnosis

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